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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,492	DIETRICH ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15,18-20,33-44 and 48-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15,18-20,33-44 and 48-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Humera N. Sheikh
HUMERA N. SHEIKH
PATENT EXAMINER
TC-1600

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Amendment and Response after Non-Final Office Action, Applicant's Arguments/Remarks and the request for extension of time (1 month-granted), all filed 06/01/06 is acknowledged.

Claims 11-15, 18-20, 33-44 and 48-60 are pending in this action. Claims 11-15, 18-20 and 33-44 have been amended. New claims 48-60 have been added. Claims 1-10, 16, 17, 21-32 and 45-47 have been previously cancelled. Claims 11-15, 18-20, 33-44 and 48-60 stand rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11-15, 18-20, 33-43 and 48-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benton *et al.* (U.S. Pat. No. 4,876,094) in view of Wong *et al.* (U.S. Pat. No. 6,120,803).

The instant invention is drawn to an oral solid active compound unit comprising a microsphere, the microsphere comprising: a matrix comprising a mixture of at least one fatty alcohol and at least one solid paraffin; and an acid-labile active compound, selected from the group consisting of an acid-labile proton pump inhibitor, a salt of an acid-labile proton pump inhibitor with a base, and a hydrate of a salt of an acid-labile proton pump inhibitor with a base, wherein said acid-labile active compound is present in said matrix. The instant invention is also drawn to an oral solid active compound unit comprising a microsphere, the microsphere comprising: a matrix comprising a mixture of at least one fatty acid ester or at least one triglyceride, and at least one solid paraffin; and an acid-labile active compound, selected from the group consisting of an acid-labile proton pump inhibitor, a salt of an acid-labile proton pump inhibitor with a base, wherein said acid-labile active compound is present in said matrix.

Benton *et al.* ('094) teach a dual coated liquid dosage formulation comprising dosage form cores such as matrix beads/microspheres (which can be time release or controlled release devices) containing a therapeutically active compound over which there are applied two unique coatings. These two coatings enable dispersion of the coated dosage form cores in a liquid carrier by imparting stability to the dosage form (see reference column 1, line 55 – col. 2, line 20).

Suitable controlled release type dosage form cores include controlled-release matrix beads/microspheres. The matrix beads/microspheres, typically are formed of a binder which is an insoluble material such as a soluble polymer or porous insoluble polymer or a wax which is intimately mixed with the therapeutically active compound (col. 3, lines 8-22).

Ingestible materials useful as a binder include waxes such as paraffin, higher fatty acids, esters of fatty acids such as glyceryl tristearate, cetyl palmitate, diglycol stearate, glyceryl myristate, triethylene glycol monostearate, higher fatty alcohols such as cetyl alcohol and stearyl alcohol and high molecular weight polyethylene glycols and mixtures thereof (col. 3, lines 23-36). The dosage form cores are microspheres or matrix beads coated with two materials. Most fats or glycerides include minor percentages of sterols, hydrocarbons, tocopherols and other non-glyceride constituents. The fats or glycerides can include mono-, di-, or triglycerides (col. 3, line 67 – col. 4, line 14). The binder can comprise as little as 5 or 10% of the core to better than 90% of the core (col. 3, lines 37-46). These amounts read on the amounts of fatty alcohol and solid paraffin claimed by Applicant in claims 54-60. Moreover, with regards to amounts, the Examiner notes that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this instance, prior art teaches a similar formulation comprising similar amounts of fatty alcohols, fatty acid esters, waxes and the like.

Alternative to a homogenous mixture, a matrix bead/microsphere can be a core mixture of larger fragments of therapeutically active compound together with binder. In another variation, the binder can envelop a fragment of therapeutically active substance forming a microsphere, which is essentially a microcapsule. Assorted and various matrix bead and microsphere configurations are suitable provided they do not substantially exceed 1400 micron diameter (col. 3, lines 47-59).

The dual coated microspheres/matrix beads are preferred dosage forms and have a size range of 15-300 μm (col. 5, lines 48-54). This range meets Applicant's claimed range of 50-500 μm. The controlled release microspheres/matrix beads can be prepared by microencapsulation processes including prilling, pan coating, granulation fluidization processes and other processes (col. 5, lines 60-66).

Therapeutically active ingredients are taught at column 6, lines 41-50. Active ingredients taught include theophylline, antihistamines, cold formulations, analgesics, amino acid supplements, vitamins (*i.e.*, vitamin C), geriatric drugs, antidepressants and the like.

Benton *et al.* teach liquid dosage formulations. Benton *et al.* do not teach solid formulations and do not teach an active compound being an acid-labile proton pump inhibitor or a salt of an acid-labile proton pump inhibitor with a base or a hydrate of a salt of an acid-labile proton pump inhibitor with a base.

Wong *et al.* ('803) teach a prolonged release active agent solid dosage formulation adapted for gastric retention. The dosage formulation includes coated microspheres of an active agent or microspheres of an active agent and adjuvant, wherein especially suitable active agents

are active agents for the localized treatment of gastric acidity and gastrointestinal disorders (*i.e.*, duodenal/peptic ulcers; chronic gastritis) such as omeprazole and lansoprazole (see reference column 18, line 1 – col. 20, line 12). Additional active agents include proteins, steroids, antidepressants, analgesics, antihistamines and the like.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds, such as omeprazole or lansoprazole taught by Wong *et al.* within the dosage formulation of Benton *et al.*, because Wong *et al.* teach that the active agents (*i.e.*, omeprazole, lansoprazole) are especially useful in their invention for the localized treatment of gastric acidity and gastrointestinal disorders, such as duodenal ulcers, peptic ulcers and chronic gastritis. The expected result would be an improved and effective proton pump inhibiting dosage formulation for the treatment of gastrointestinal disorders and conditions.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Benton *et al.* (U.S. Pat. No. 4,876,094) in view of Wong *et al.* (U.S. Pat. No. 6,120,803) as applied to claims 11-15, 18-20, 33-43 and 48-60 above and further in view of Steber (U.S. Pat. No. 5,213,810).

The teachings of Benton *et al.* and Wong et al. are delineated above. Benton *et al.* teach paraffin (col. 3, line 27). Benton *et al.* do not teach the paraffin, ozocerite.

Steber ('810) teaches stable microsphere compositions and methods of making microsphere compositions containing a fat, wax or mixture thereof; a biologically active protein, peptide or polypeptide; and an oil, semi-soft fat, fatty acid derivative or mixture thereof (see

Abstract and Claims). Suitable natural waxes taught include fossil or earth waxes such as ozocerite and petroleum waxes such as paraffin, microcrystalline (col. 2, lines 60-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the particular wax, ozocerite of Steber within the dosage formulations of Benton *et al.* One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because Steber teach that suitable and effective waxes used in their microsphere compositions include naturally derived waxes of fossil or earth waxes, such as ozocerite. The expected result would be an improved and beneficial proton pump inhibiting dosage formulation for treating an array of gastrointestinal disorders.

Response to Arguments

Applicant's arguments filed 06/01/06 have been fully considered but they are not persuasive.

35 U.S.C. §103(a) rejection of claims 11-15, 18-20 and 33-43 over Benton et al. ('094) in view of Wong et al. ('803):

Applicant argued, "Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a prima facie case of obviousness against the presently rejected claim. Benton et al. is directed to an acidic liquid dosage formulation where the active compound is contained in the matrix of a dual-coated microsphere (col. 1, lines 13-15; col. 3, lines 1-5; col. 13, lines 45-51). Benton requires the dual-coating in order to prevent release of the active compound into the acidic liquid carrier. See col. 12, lines 60-68; col. 16, lines 11-18. Benton et al. further requires that the acidic carrier comprise a sugar-based acidic liquid in order to achieve restricted release of the active compound. See col. 13, lines 46-51 and claim 1.

Wong et al. is directed to a dosage form that is retained in the stomach for prolonged periods of time to achieve prolonged delivery of an active agent in the stomach (col. 5, lines 29-33). Wong et al. achieves prolonged delivery in the stomach by providing a solid ingestible dosage form including an active agent and a polymer matrix formed of a mixture of a swellable, water soluble polymer that expands when in contact with fluids in the stomach and a water-insoluble hydroattractant (col. 5, lines 13-15).

Wong et al. achieve prolonged retention time in the stomach by means of an insoluble band which causes the polymer matrix to retain its integrity in an expanded state (col. 5, lines 30-34).

The presently pending claims require an oral solid formulation. In contrast, Benton et al. disclose a liquid dosage formulation, which is entirely different both structurally and functionally than the presently claimed oral solids.

Wong et al. do not remedy this deficiency. In particular, the Wong et al. reference is directed to a completely non-analogous art area. Wong et al. is concerned with providing prolonged delivery of an active compound in the stomach by means of an insoluble band around a polymer matrix. In contrast, the presently claimed formulations deliver their active compounds in the intestines, because the claimed proton pump inhibitor actives decompose in an acidic environment (page paragraph such as is found the stomach. Therefore, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds directed toward prolonged delivery in the stomach taught by Wong et al. with the liquid dosage formulations of Benton et al. to arrive at applicants' oral solid formulation for delivery in the intestines. Moreover, there is absolutely no suggestion that would motivate a person of ordinary skill in the art to combine the liquid dosage formulation of Benton et al. with the formulation described in Wong et al. which is concerned with providing prolonged delivery of an active compound in the stomach, to arrive at the presently claimed solid dosage formulation which deliver their active compounds in the intestines.

Accordingly, reading Benton et al. in view of Wong et al. fails to show a suggestion or incentive that would motivate a person of ordinary skill in the art to combine as required by *In re Fine.*

Additionally, neither Benton et al. nor Wong et al., taken alone or together, teach or suggest an active compound unit comprising a microsphere, where the microsphere matrix contains at least one solid paraffin and at least one fatty alcohol; or contains at least one fatty acid ester or at least one triglyceride, and at least one solid paraffin."

Applicant's argument that 'Benton et al. is directed to a liquid dosage formulation whereas the instant invention is drawn to a solid formulation' has been considered, but was not found to be persuasive. Admittedly, while Benton et al. is, in essence, drawn to a liquid dosage formulation, the secondary reference of Wong et al. are relied upon to demonstrate that it is known to formulate solid dosage formulations comprising active agents, such as the proton pump inhibitors (PPI's) omeprazole and lansoprazole (see Wong et al. column 20, lines 3-12). Examiner notes the active agents of Wong et al. can also be in liquid, solid or semisolid form (col. 17, lines 23-24). Thus, the prior art meets the claim limitation of an oral, solid active compound unit. Applicant's argument that "The Wong et al. reference is directed to a completely non-analogous art area and that Wong et al. is concerned with providing prolonged delivery of an active compound in the stomach whereas, the presently claimed formulations deliver their active compounds in

the intestines" has been considered but was not found persuasive since Wong et al. is directed to an analogous art area. Namely, Wong et al. are also directed to solid dosage formulations, such as tablets that comprise active agents, particularly PPI's. While the structure of Wong et al. may vary slightly from that claimed, it is not necessary that Wong et al. teach the exact same structure since Wong et al. are merely relied upon for the teaching of the use of solid dosage formulations (i.e., tablets) comprising PPI's. With regard to Applicant's argument that the 'Wong et al.'s formulations are for delivering active compound to the stomach, whereas the instant invention is delivered to the intestines', this argument was not persuasive since the arguments addressed do not establish the scope of claims being presented. Applicants do not claim delivery of the active compound unit to the intestines. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Absent a showing of unexpected results attributable to the claimed solid active compound units, the prior art essentially meets the limitations claimed by Applicant.

It remains the position of the Examiner that given the combined teachings of Benton et al. and Wong et al., the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

35 U.S.C. §103(a) rejection of claims 11-15, 18-20 and 33-44 over Steber ('810) in view of Wong et al. ('803):

Applicant argued, "Applicants submit that neither the Steber reference nor the Wong et al. references cited in the rejection of claims 11-15, 18-20, and 33-44, taken alone or in combination, establish a prima facie case of obviousness against the presently pending claims. It would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds taught by Wong et al. and noted above in Section C above, with the dosage formulations of Steber to arrive at the presently pending claims 11-15, 18-20, and 33-44. Steber is directed to a liquid dosage formulation of controlled release microspheres for parenteral administration to an animal. See Abstract; col. 2, lines 30-31. Further, Steber describes microspheres that comprise a fat or

wax or mixtures thereof, and about 1% to 30% of an semi-soft fat, fatty acid derivative or mixtures thereof. Specifically, in Examples Steber describes microspheres that contain glyceryl tristearate which is the "fat or wax" component, and Miglycol (a neutral triglyceride oil), glyceryl distearate (a fatty acid ester), or triacetin (glycerol triacetate) which is the "oil, semi-soft fat, or fatty acid derivative" component. Examples 8 and 9 describe microspheres produced from glyceryl tristearate alone and stabilized microspheres produced from glyceryl tristearate and neutral triqlyceride oil.

The presently pending claims, as noted above in Section A, the arguments of which are hereby incorporated by reference in their entirety, require an oral solid formulation. In contrast, Steber is directed to a formulation for parenteral administration to an animal, which is entirely different both structurally and functionally than the presently claimed oral solids. Accordingly, Steber does not teach the presently claimed oral solid formulations.

Wong et al. do not remedy this deficiency. In particular, the Wong et al. reference is directed to a completely non-analogous art area. Wong et al. is concerned with providing prolonged delivery of an active compound in the stomach by means of an insoluble band around a polymer matrix. In contrast, the presently claimed formulations deliver their active compounds in the intestines, because the claimed proton pump inhibitor actives decompose in an acidic environment (page paragraph 3) such as is found in the stomach.

Therefore, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds directed toward prolonged delivery in the stomach taught by Wong et al. with the parenteral administration of Steber to arrive at applicants' oral solid formulation for delivery in the intestines.

Moreover, there is absolutely no suggestion that would motivate a person of ordinary skill in the art to combine the parenteral administration of Steber with the formulation described in Wong et al. which is concerned with providing prolonged delivery of an active compound in the stomach, to arrive at the presently claimed solid dosage formulation which deliver their active compounds in the intestines. Accordingly, reading Steber in view of Wong et al. fails to show a suggestion or incentive that would motivate a person of ordinary skill in the art to combine as required by *In re Fine*. Additionally, neither Steber nor Wong et al., taken alone or together, suggest an active compound unit comprising a microsphere, where the microsphere matrix contains a mixture of at least one solid paraffin and at least one fatty alcohol as claimed in present claims 11, 13-15, 33-41 and 44; or contains a mixture of a least one fatty acid ester or at least one triglyceride, and at least one solid paraffin, as claimed in the present claims 12, 42, and 43.

Further, none of the Examples of Steber illustrate a microsphere containing at least one solid paraffin as claimed in the present claims, let alone a microsphere containing at least one solid paraffin and at least one fatty alcohol as claimed in present 33-41, 44, 48, and 50-60. Specifically, the glyceryl tristearate exemplified in Steber is not "solid paraffin" and none of the triglyceride oil, glyceryl distearate, and glycerol triacetate, exemplified in Steber, are fatty alcohols.

Accordingly, even combining Steber with Wong fails to teach or suggest all of the limitations of the presently pending claims as required by In re Wilson and falls short of beginning to establish a prima facie case of obviousness."

Applicant's arguments have been carefully considered and were found to be persuasive. Accordingly, the rejection of claims 11-15, 18-20 and 33-44 over Steber in view of Wong et al. has been withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Humera N. Sheikh
Patent Examiner
Art Unit 1615
August 21, 2006

hns